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Medial Prefrontal and Subcortical Mechanisms Underlying the Acquisition of Motor and Cognitive Action Sequences in Humans

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Summary

The anterior medial prefrontal cortex (AMPC) in humans is involved in affect and in regulating goal-directed behaviors. The precise function of the AMPC, however, is poorly understood. Using magnetic resonance imaging, we found that bilateral regions in the AMPC were selectively recruited to compute the reliability of subjects' expectations that developed when subjects were learning sequences of cognitive tasks. In contrast, regions similarly recruited in learning sequences of motor acts were found in the ventral striatum. Our results show that beyond the execution of motor acts, the AMPC is selectively engaged in computing the relevance of cognitive goals that subjects intend to achieve. This indicates that the fronto-striatal circuit, including the ventral striatum and AMPC, subserves hierarchically distinct evaluative processes mediating the human ability to build behavioral plans, ranging from motor to cognitive action plans.

Introduction

The prevailing view about the role of the anterior medial prefrontal cortex (AMPC) in humans is that it regulates affective and goal-directed behaviors (Cummings, 1993; Damasio, 1996; Devinsky et al., 1995). Some evidence in support of this view comes from patients with lesions of the ventromedial prefrontal cortex (including the AMPC) who are impaired in evaluating future positive and negative consequences of their actions in decision-making tasks (Bechara et al., 1996, 1998). Other evidence comes from neuroimaging studies revealing that in normal subjects metabolic activity in the AMPC is modulated by various emotional and cognitive manipulations (review in Bush et al., 2000; Simpson et al., 2001).

Further, the AMPC covers the medial wall of the anterior prefrontal cortex rostral to the corpus callosum and is organized in a distinctive network of tightly interconnected areas mainly including cytoarchitectonic Brodmann's areas 24, 25, 32, and 10 (Ongur and Price, 2000). When compared with other frontal sectors, this region forms a distinct fronto-striatal loop circuit and predominantly projects to the ventral striatum (VS) (Alexander et al., 1986; Haber et al., 1995), a subcortical structure that in humans and animals supports behaviors based on reward and reinforcement (Apicella et al., 1991; Delgado et al., 2000; Schultz et al., 1992) and that mediates the acquisition of motor action plans (Doyon et al., 1996; Grafton et al., 1995; Jueptner et al., 1997; Schultz et al., 1992; Shidara et al., 1998). In addition, both VS and AMPC are important projection sites of dopaminergic neurons that are known to implement motivational and reinforcement mechanisms (Lewis et al., 1988; Robbins and Everitt, 1996; Schultz, 1997).

The specific function of the human AMPC, however, is poorly understood and remains elusive. In the present study, we investigated the hypothesis, based on the known anatomical and functional links between the AMPC and VS, that the AMPC and VS subserve similar functions but at different levels of representation. Previous studies in monkeys revealed that neurons in the VS process expectations of behaviorally significant events (including reward signals), the actual occurrences of those events, and have access to related error prediction signals originating from dopaminergic neurons when subjects are building and executing motor action sequences (see reviews in Graybiel and Kimura, 1995; Schultz et al., 1995; Shidara et al., 1998). Consistent with neuroimaging studies on motor sequence learning in humans (Doyon et al., 1996; Grafton et al., 1995; Jueptner et al., 1997), these results indicate that the VS plays a pivotal role in driving the acquisition of motor action plans by evaluating the reliability of subjects' expectations that develop when subjects are building such motor action sequences (Schultz et al., 1997). We postulated that the AMPC would similarly drive the acquisition of more abstract action sequences that have no instantiation in the motor domain.

More specifically, we hypothesized that the AMPC would drive the acquisition of *cognitive action sequences*, i.e., fixed sequences of cognitive tasks or goals that are not reducible to fixed sequences of body movements or motor acts (Dehaene and Changeux, 1997; Graybiel, 1997). In cognitive action plans, subjects execute fixed sequences of cognitive tasks, producing a series of motor acts that are contingent upon each behavioral context. Such cognitive action sequences are frequently required in human activities, e.g., in problem-solving, reasoning, or simply when humans carry out procedures such as cooking recipes or devising game strategies.

Our assumption is supported by the evidence that the anterior prefrontal cortex implements more complex cognitive representations than the striatum and subserves processes underlying task/goal management (Fletcher and Henson, 2001; Koechlin et al., 1999; Miller and Cohen, 2001). Moreover, recent findings have shown that the AMPC is selectively involved when subjects perform predictable sequences of cognitive tasks (Koechlin et al., 2000). Thus, given that the VS is involved in evaluating the reliability of subjects' expectations that develop when subjects are building *motor* action sequences, we hypothesized that the AMPC would be similarly involved in evaluating the reliability of subjects'

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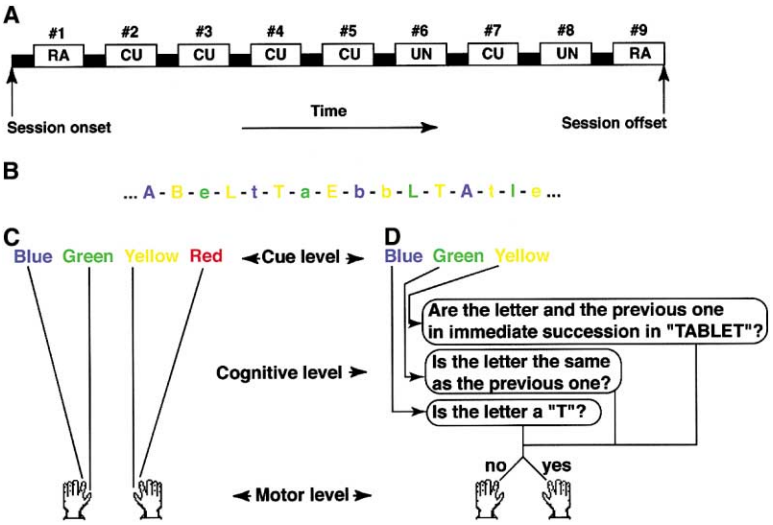

Figure 1. Experimental Protocols

(A) A typical learning session divided into nine experimental blocks (numbered from #1 to #9) intermixed with baseline blocks (black rectangles). Each session began and ended with a random condition (RA, blocks #1 and #9) in which subjects performed finger movements (motor experiment) or cognitive tasks (cognitive experiment) in a random order. In the cued condition (CU, blocks #2, #3, #4, #5, and #7), subjects performed finger movements or cognitive tasks in a fixed order as indicated by visual cues. In the uncued condition (UN, blocks #6 and #8), no visual cue was presented and subjects had to perform finger movements or cognitive tasks in the same order as in the preceding cued blocks. In the baseline condition, subjects performed a simple detection task. (B) A typical series of stimuli presented in the cued condition. Visual cues were the color of letters and were presented either in fixed sequences (cued condition, sequence length, 4) or in a random order (random condition). In the uncued condition, colors were turned off. The color cue indicated the finger that subjects had to move (motor experiment [C]) or the task they had to perform on each letter (cognitive experiment [D]). The proportions of left and right responses were the same in all blocks by using an additional cue color in the motor experiment (red) and by pseudo-randomizing yes/no response in the cognitive experiment. Tasks in the cognitive experiment were either a 0-back («Is the letter a T?»), a 1-back («Is the letter the same as the previously presented one?»), or a variant 1-back («Are the letter and the previously presented one in immediate succession in the word tablet?») letter matching tasks (Cohen et al., 1997; Koechlin et al., 1999). Note that letter stimuli were randomized so that in the cognitive experiment, motor responses remained unpredictable in all blocks, even when subjects were repeating the same sequence of cognitive tasks.

expectations that develop when subjects are learning cognitive action sequences.

From a theoretical point of view, the functional segregation we hypothesized was based on the premise that similar evaluation processes should a priori occur at different levels of action representation, i.e., in the motor versus cognitive domains, in order that matches or mismatches between a subject's behavior and external events could be interpreted internally as the correct or incorrect selection of either a motor response or a cognitive goal (Dehaene and Changeux, 1997). An alternative hypothesis would be that the VS and AMPC might implement distinct learning processes, like implicit versus explicit learning processes (Graf and Schacter, 1985), that might be differentially involved in learning motor and cognitive action sequences.

Functional magnetic resonance imaging (fMRI) was used to test our hypothesis. Eight neurologically normal subjects were scanned while learning either motor or cognitive sequences in an explicit learning paradigm (Figure 1). In the motor experiment, subjects had to learn sequences of finger movements they were instructed to execute in response to fixed sequences of visually presented cues. In the cognitive experiment, in contrast, the same subjects had to learn sequences of distinct cognitive tasks they were instructed to perform in response to the same sequences of visual cues (cognitive tasks were letter backward matching tasks). In addition, a given sequence of cognitive tasks was always associated with distinct letter stimuli and motor responses so that the response to cognitive task sequences, unlike motor task sequences, did not require a fixed sequence of finger movements. In both experiments, subjects first learned the motor and cognitive sequences in successive blocks with visual cues, and then proceeded to alternating blocks with or without cues. When cues were removed, no external signal provided information about the reliability of subjects' expectations and performance.

We then reasoned that the brain structures that compute the reliability of subjects' expectations that develop when subjects are building action sequences would exhibit a *cue-learning effect*, i.e., activations increasing gradually above baseline while subjects were learning action sequences using visual cues but falling back to the baseline whenever cues were removed (i.e., whenever subjects received no external signal or feedback about their expectations). This cue-learning effect modeled the increasing consistency (i.e., the number of matches) between the actions that subjects increasingly expected to perform during learning and the subsequent presentation of associated cues (see Experimental Procedures for details). Previous brain imaging studies reported increasing activations in the VS during motor sequence learning (Grafton et al., 1995) and in response to positive reinforcers (Delgado et al., 2000). We then predicted that brain regions exhibiting cue-learning effects in the motor experiment only would be found in the VS, whereas brain regions exhibiting cue-learning effects in the cognitive experiment only would be found in the AMPC.

Results

Behavioral Results

The behavioral data showed that in each experiment, reaction times (RTs) decreased significantly over time in the first four cued blocks (linear trends, both $F[1, 7] > 21.4$, $p < 0.003$) and then stabilized asymptotically in the subsequent cued and uncued blocks (linear trends,

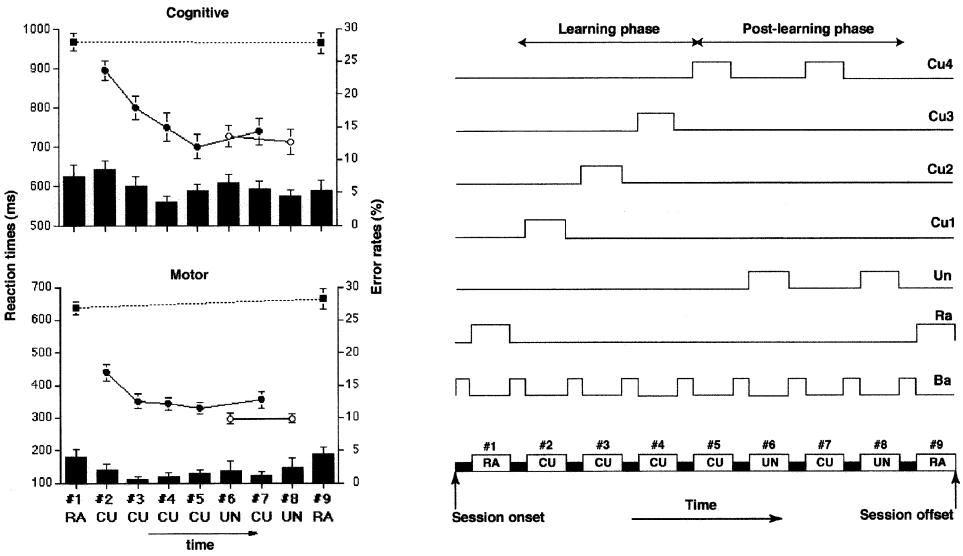

Figure 2. Behavioral Performance

Left, reaction times (symbols, mean ± SE in milliseconds) and error rates (bars, mean ± SE in percentage) across experimental conditions averaged over the learning sessions in the cognitive (top) and motor (bottom) experiments (see Figure 1 for notations). Right, schematic diagram displaying the covariates of interests included in the multiple regression used to analyze fMRI data. Bottom right, a typical learning session. Top right, covariates (Ba, Ra, Cu1, Cu2, Cu3, Cu4, and Un) shown before being convolved by the canonical hemodynamic response function (see Experimental Procedures). The two random blocks #1 and #9 were collapsed together, as were the two cued blocks #5 and #7, and the two uncued blocks #6 and #8, because behavioral performances were unchanged in these block pairs.

$F < 1$), when subjects were performing the cognitive tasks or movements in fixed sequences (see Figure 2). In contrast, no significant differences in performance were observed while subjects were executing random series of finger movements or cognitive tasks in two random conditions performed before and after each learning session (both $F[1, 7] < 1.6$, $p > 0.24$). The unchanged performance between the two random conditions indicated that no associative learning occurred between cues and associated movements or tasks while subjects were learning action sequences. Thus, the behavioral results confirmed that beyond any practice or fatigue effects, subjects gradually anticipated the presentation of visual cues and began to generate motor and cognitive sequences internally over the time course of the learning sessions. Finally, when cues were removed, no increases in error rates and RTs were observed relative to the cued condition, indicating that motor and cognitive sequences were accurately internalized and generated. More precisely, in the cognitive experiment, no significant difference in RTs were observed ($F < 1$), whereas in the motor experiment, RTs were significantly larger in the cued than in the uncued conditions ($F[1, 7] = 13.2$, $p < 0.01$). This difference simply reflected that in the cognitive experiment, evaluating the anticipated task and computing the motor response associated with the task could occur at the same time, whereas in the motor experiment, evaluating the anticipated movement could occur only after motor preparation, thereby delaying motor execution.

fMRI Results

First of all, analyses were carried out to confirm that motor and cognitive sequences were acquired and processed as distinct internal representations. Thus, we tested that distinct brain regions were engaged in executing fixed cognitive and motor sequences independently of the presentation of visual cues. In each experiment, we computed regions exhibiting a *sequence effect*: in the motor experiment, the sequence effect was computed as larger activations relative to baseline while subjects were performing fixed motor sequences once learning occurred and even in the absence of visual cues (see Experimental Procedures). Thus, in accordance with previous brain imaging studies on motor control (e.g., Gordon et al., 1998), the motor sequence effect contrasted, in response to similar visual signals, the internal generation of known sequences of distinct motor acts with the internal repetition of the same motor act (baseline). In the cognitive experiment, the sequence effect was computed in the same way as larger activations in postlearning cued and uncued conditions relative to baseline, but also relative to the random condition. Postlearning cued and uncued conditions in the cognitive experiment were directly compared to the random condition, because in contrast to the baseline, all these conditions required subjects to perform the same cognitive tasks. Thus, the cognitive sequence effect excluded regions involved only in executing or switching between those cognitive tasks, but identified regions engaged in processing sequential patterns underlying cognitive sequences.

Using a fixed-effect model, the regions showing sequence effects jointly in the cognitive and motor experiments included bilaterally the inferior parietal lobules (BA 40) and lateral premotor cortices (BA 6) (Figure 3). As expected, however, we found motor- and cognitive-specific sequence effects: sequence effects restricted

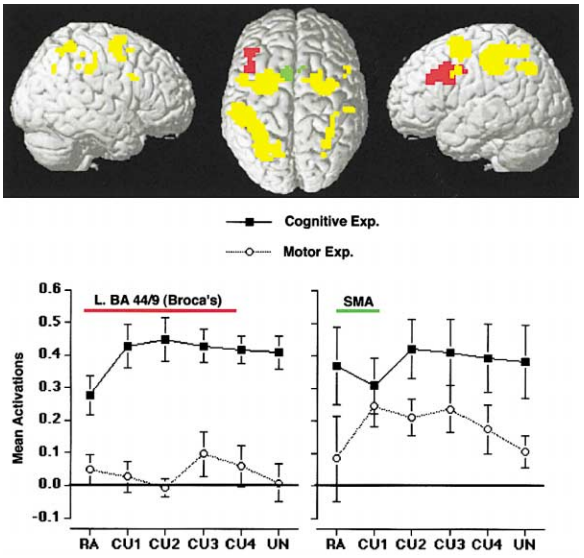

Figure 3. Topography (Top) and Activation Profiles (Bottom) of Sequence Effects

Yellow, sequence effects jointly in the motor and cognitive experiments. Green, sequence effects in the motor experiment only (activation peaks at $x, y, z = -4, 8, 64$, SMA). Red, sequence effects in the cognitive experiment only (activation peaks at $x, y, z = -48, 12, 32$ and $-44, 24, 28$; BA 44 and 9). Graphs show the mean activations computed over each region (averaged regression coefficients $\pm$ SEs across subjects) in the random (Ra = blocks #1 and #9 collapsed together), the cued (Cu1 = block #2, Cu2 = block #3, Cu3 = block #4, Cu4 = blocks #5 and #7 collapsed together), and the uncued (Un = block # 6 and #8 collapsed together) conditions relative to the baseline. *y* axis origins represent the mean activations in the baseline condition. Closed squares, cognitive experiment. Open circles, motor experiment.

to the motor experiment were found in the supplementary motor area (SMA), whereas sequence effects restricted to the cognitive experiment were found in the left inferior and middle frontal gyri (BA 44/9, Broca's area). In the motor experiment, the activation in Broca's area remained virtually at the baseline level in all conditions, whereas SMA activations increased significantly above the baseline level when subjects were performing fixed motor sequences even in the absence of visual cues (Figure 3, bottom). In contrast, in the cognitive experiment, the activation in Broca's area, but not in the SMA, was larger while subjects performed fixed rather than random cognitive sequences. This dissociation of motor and cognitive sequence effects was confirmed by subsequent random-effect analyses (see Experimental Procedures). Overall, these data show that distinct brain regions were engaged in processing sequential patterns underlying motor and cognitive sequences.

Next, we investigated the regions that were involved in evaluating subjects' expectations that developed during sequence learning, i.e., regions exhibiting cue-learning effects: activations increasing gradually above baseline while subjects were learning action sequences using visual cues but falling back to the baseline whenever cues were removed (see Introduction and Experimental Procedures).

Using a fixed-effect model, we first computed cue-learning effects jointly in both experiments. Because in both experiments visual cues were used to induce sequence learning, joint cue-learning effects identify brain structures involved in matching subjects' cue expectations with the actual occurrences of those cues. Joint cue-learning effects were observed in all structures composing the anterior medial fronto-striatal circuit (Alexander et al., 1986), including the AMPC, VS, globus pallidus/putamen, and thalamus (Table 1; Figures 4, 5E, and 5F). Additional joint cue-learning effects were found in left premotor cortex.

Second, we identified regions exhibiting cue-learning effects in the motor experiment, but not in both the motor and cognitive experiments (see Experimental procedures for details). As predicted, this analysis revealed one region within the anterior medial fronto-striatal circuit, namely the VS (see Table 1, and Figures 4 and 5A): in this region, a significant interaction was found between the motor and cognitive response profiles ($F > 3.84$, $p < 0.05$, uncorrected). In the motor experiment, the magnetic resonance (MR) signal gradually increased above baseline in the cued condition during learning, and returned to the baseline in the uncued condition. In contrast, in the cognitive experiment, the MR signal remained below the baseline in all conditions (Figure 5A). Additional motor-specific cue-learning effects were found in the left insular cortex.

Third, we tested for regions exhibiting cue-learning effects in the cognitive experiment but not in both the motor and cognitive experiments. As predicted, we found bilateral regions in the AMPC (rostral anterior cingulate cortex BA 32/24; Table 1, Figures 4, 5B–5D). In those regions, we observed again a significant interaction between the motor and cognitive response profiles ($F > 3.84$, $p < 0.05$, uncorrected): in the cognitive experiment, the MR signal gradually increased above baseline in the cued condition during learning, and returned to baseline in the uncued condition, whereas in the motor experiment, the MR signal remained below baseline (Figures 5B–5D). Cue-learning effects restricted to the cognitive experiment were also seen in the left dorsal putamen/globus pallidus, but no significant interaction was observed in this region between the motor and cognitive response profiles ($F < 3.84$, $p > 0.05$). No additional cue-learning effects specific to the cognitive experiment were found.

Subsequent random-effect analyses confirmed the previous results (see Experimental Procedures). The same patterns of joint, motor-, and cognitive-specific cue-learning effects were observed (Figure 5). Moreover, in order to further assess the functional segregation between the VS and AMPC, the mean cue-learning effects computed over each region exhibiting motor- and cognitive-specific cue-learning effects were entered in a 2×2 repeated measure ANOVA with regions (VS versus AMPC) and experiments (motor versus cognitive) as within-subjects factors. As expected, the ANOVA revealed a significant interaction between both factors ($F[1, 7] = 6.28$; $p < 0.041$), confirming the segregation of motor and cognitive cue-learning effects observed between the VS and AMPC.

Since in the present study an explicit learning procedure was used to induce sequence learning, we con-

Table 1. Cue-Learning Effects in the Anterior Medial Prefrontal Cortex and the Basal Ganglia

		Statistical Effects (Z Scores Relative to the Baseline, Fixed-Effect Model)[c]							
		Random Blocks (Ra)		First cued block (Cu1)		Last cued blocks (Cu4)		Uncued blocks (Un)	
Brain Regions[a]	Talairach Coordinates[b]	Cogn. Exp.	Motor Exp.	Cogn. Exp.	Motor Exp.	Cogn. Exp.	Motor Exp.	Cogn. Exp.	Motor Exp.
Cognitive Only									
L ant. cingulate	−20, 44, 0	−1.4	−4.0	0.9	−1.9	*5.4*	−0.3	0.9	−0.8
R ant. cingulate	24, 40, 12	−0.7	−2.1	−1.8	−0.8	*5.6*	−0.7	0.9	−1.5
L putamen/GP	−24, 4, 12	0.3	−3.4	−1.0	−0.6	*4.7*	*1.2*	1.2	−0.2
Motor Only									
L ventral striatum	−8, 16, −16	−3.2	−0.7	−2.3	−3.6	0.4	*4.2*	−1.6	−0.4
	−24, 4, −16	−6.2	−3.3	−0.8	−2.1	−0.1	*3.2*	−3.6	−1.7
Cognitive and Motor									
R ant. cingulate	8, 44, 0	−4.2	0.1	−2.4	−3.7	*3.7*	*2.2*	0.3	0.4
L ventral striatum	−16, 16, −8	−2.1	−2.7	−2.8	−2.3	*3.1*	*2.3*	1.0	−1.6
L thalamus	−12, −8, 4	−0.8	−3.7	1.7	−0.1	*4.1*	*2.1*	1.2	−1.0
L GP/putamen	−20, −12, 16	−1.0	−4.0	0.1	−0.5	*3.4*	*1.7*	1.4	−1.0
R GP/putamen	24, 4, 8	−1.6	−4.1	−1.6	−0.3	*2.7*	*1.9*	0.7	−1.6
	28, −16, 0	−3.6	−5.2	−1.9	−0.3	*2.0*	*1.9*	−1.8	−1.1

[a] L, left; R, right; ant, anterior; GP, globus pallidus.
[b] Coordinates of maxima in contrast Cu4 minus baseline (italics). Activation peaks were virtually the same in fixed- and random-effect models.
[c] Ra, Cu1, Cu4, and Un are covariates described in Experimental Procedures. Exp., experiment. Cogn., cognitive.

trolled for brain regions implementing explicit control processes that could also drive sequence learning. Explicit control processes were assumed to be engaged maximally at the beginning of learning, then would disengage gradually while learning proceeded and behavior became more automatic. Thus, brain regions implementing explicit control processes were assumed to exhibit a *controlled-learning effect*, i.e., larger activations at the beginning of learning relative to the baseline and random conditions that subsequently decreased while learning proceeded (see Experimental Procedures). Note that the controlled-learning effect identified only regions with larger activations at the beginning of learning relative to the random condition, thereby excluding activations that varied in the same way as behavioral performance or task difficulty.

Joint controlled-learning effects over both experiments were found bilaterally in the lateral anterior prefrontal cortex (Brodman's Area BA 9/46/10, see Figure 6). Motor-specific controlled learning effects were observed bilaterally in the inferior parietal lobules and premotor cortices. Cognitive-specific controlled learning effects were found in the right anterior prefrontal cortex (BA 9/46/10). This pattern of results was obtained using a fixed-effect model and then confirmed by a subsequent random-effect analysis (see Experimental Procedures). The only exception was a right lateral frontopolar region exhibiting a significant motor-specific controlled-learning effect in the fixed- but not in the random-effect model.

Discussion

In the present study, we tested the hypothesis that the AMPC is recruited to evaluate the expectations of future events that subjects develop for building cognitive sequences, in the same way that the VS is engaged in the acquisition of motor sequences. These evaluation processes were identified and localized by computing cue-learning effects. In accordance with our assumption, cue-learning effects were found in both the VS and AMPC. Moreover, the results confirm the predicted functional segregation between the two brain regions, because motor-specific cue-learning effects were observed in the VS, whereas cognitive-specific cue-learning effects were found in the AMPC.

One might argue that cue-learning effects identify not only processes that evaluate expectations during sequence learning but also associative learning processes that might occur between cues and associated movements or tasks. However, as shown by behavioral results, no associative learning occurred in both the motor and cognitive experiments: the subjects' performances remained unchanged whenever they were cued to execute random series of motor acts or cognitive tasks. Thus, the observed cue-learning effects could not be interpreted as resulting from associative learning processes.

Behavioral data indicate that the dissociation observed between the VS and AMPC is unlikely to result from any additional mental effort required in the cognitive experiment. Indeed, a mental effort interpretation of the data would predict the greatest activations to

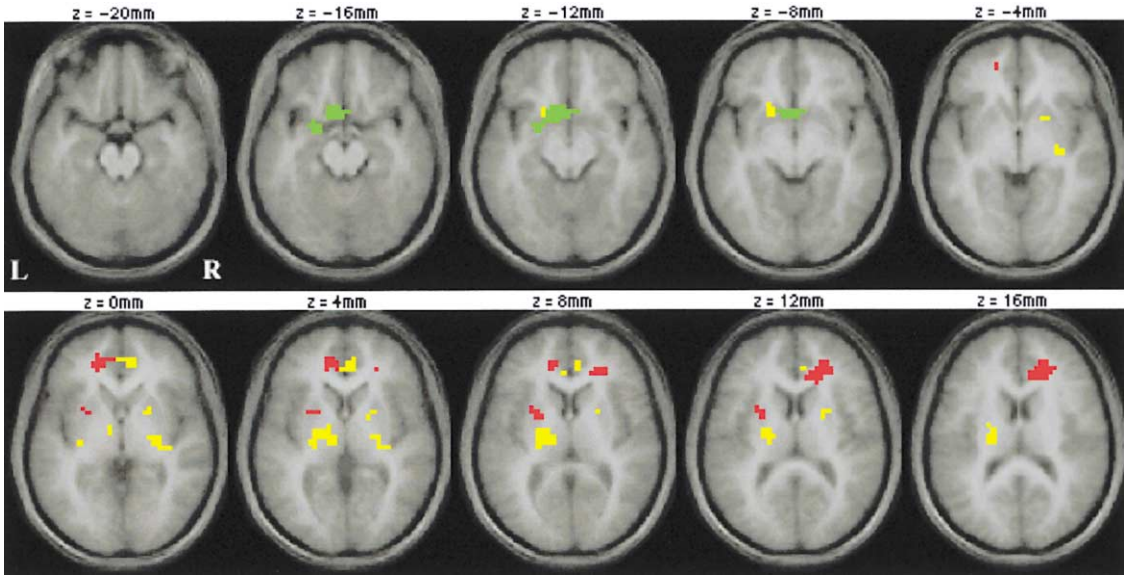

Figure 4. Topography of Cue-Learning Effects

Yellow, regions showing cue-learning effects jointly in both the motor and cognitive experiments. Green, regions showing cue-learning effects in the motor experiment only (VS). Red, regions exhibiting cue-learning effects in the cognitive experiment only (AMPC and putamen/globus pallidus). Functional activations are superimposed on anatomical axial slices averaged across subjects (neurological convention) and indexed with the vertical Talairach coordinates (*z*). Only activations in the volume of interest are shown. Additional joint and motor-specific cue-learning effects were found in left premotor ($x, y, z = -60, 0, 28$; BA 6) and left insular ($x, y, z = -48, -8, -12$) cortices, respectively.

appear in the condition showing the most altered behavioral performance (Furey et al., 1997). Because behavioral performance in the cognitive experiment was similar in the cued and uncued conditions (once learning occurred) but was significantly altered in the random conditions, the mental effort interpretation would predict the greatest activation to be observed in the random condition. However, AMPC activations relative to baseline were observed in the cued condition but neither in the uncued or random conditions, thereby ruling out a mental effort interpretation of the observed dissociation.

In the same vein, one might argue that the dissociation was observed because subjects developed sequence awareness in the cognitive but not in the motor experiment. This interpretation would be consistent with previous findings revealing that motor sequences may be acquired without awareness (Willingham et al., 1989). We ruled out this interpretation of our data, however, because learning was explicit in both experiments, i.e., subjects were explicitly instructed to learn sequences of four actions in both experiments.

Furthermore, it is unlikely that cue-learning effects observed in the VS and AMPC reflect distinct learning processes, such as implicit learning processes that might mainly occur during motor sequence learning and explicit rule-based learning processes that might be mainly involved during cognitive sequence learning (Graf and Schacter, 1985). This interpretation would predict distinct activation dynamics in the two structures, since in contrast to implicit learning processes, the engagement of explicit control processes are expected to decrease with learning. In both structures, however, activations were found to increase with learning. In addition, we found evidence that similar explicit control processes were involved while subjects were learning motor and cognitive sequences. In both experiments, activations that decreased with learning were found bilaterally in the anterior prefrontal cortex including the frontopolar cortex, a finding consistent with previous studies (Jenkins et al., 1994; Strange et al., 2001). In the motor experiment, additional decreasing activations were observed bilaterally in the inferior parietal lobules and premotor cortex, but those regions were also engaged, when subjects performed sequences of cognitive tasks. Thus, in the present study, brain activations provided no evidence that learning cognitive and motor sequences engaged distinct, explicit control processes.

Consequently, the present results provide evidence that cue-learning effects observed in the VS and AMPC reflect similar learning processes driving the acquisition of action sequences. The regional segregation between motor and cognitive cue-learning effects indicate further that the VS combines external signals and subjects' expectations in learning motor action sequences, whereas the AMPC combines external signals and subjects' expectations in learning cognitive action sequences. Indeed, the VS and AMPC were engaged relative to baseline only when successive motor acts and cognitive tasks, respectively, were internally generated *and* matched the subsequent occurrence of external cues. This finding indicates that the VS subserves processes that evaluate the relevance of planned motor acts using external signals, whereas the AMPC subserves similar processes evaluating the relevance of planned cognitive tasks.

Moreover, in the VS and AMPC, as well as in the globus pallidus and thalamus, we found additional regions exhibiting cue-learning effects regardless of

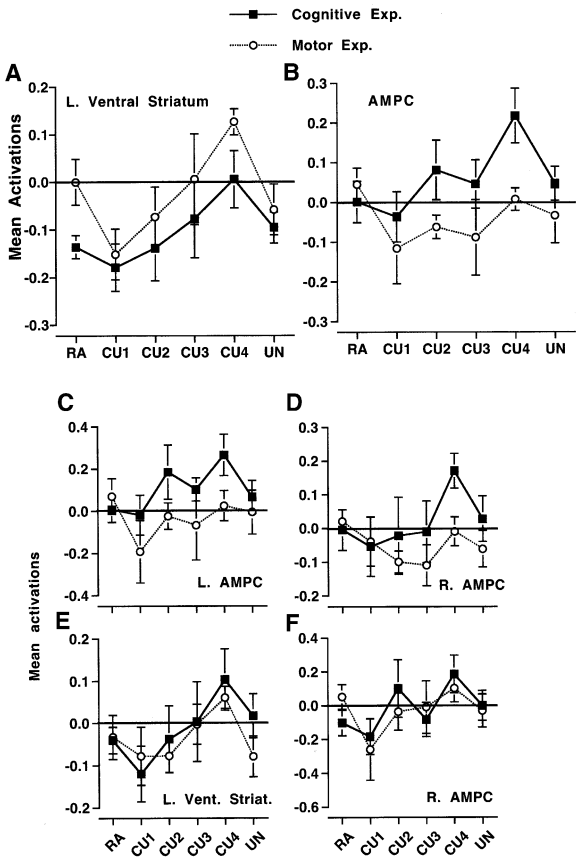

Figure 5. Activation Profiles in Regions Exhibiting Cue-Learning Effects

(A) Motor-specific effects in VS (green region in Figure 4) are shown.
(B) Cognitive-specific effects (red regions in the AMPC pooled together, see Figure 4) are shown.
(C) Cognitive-specific effects in the left AMPC (red region in Figure 4) are shown.
(D) Cognitive-specific effects in the right AMPC (red region in Figure 4) are shown.
(E and F) Joint cue-learning effects in the ventral striatum and AMPC (yellow regions in Figure 4) are shown. See Figure 3 for graph legends.

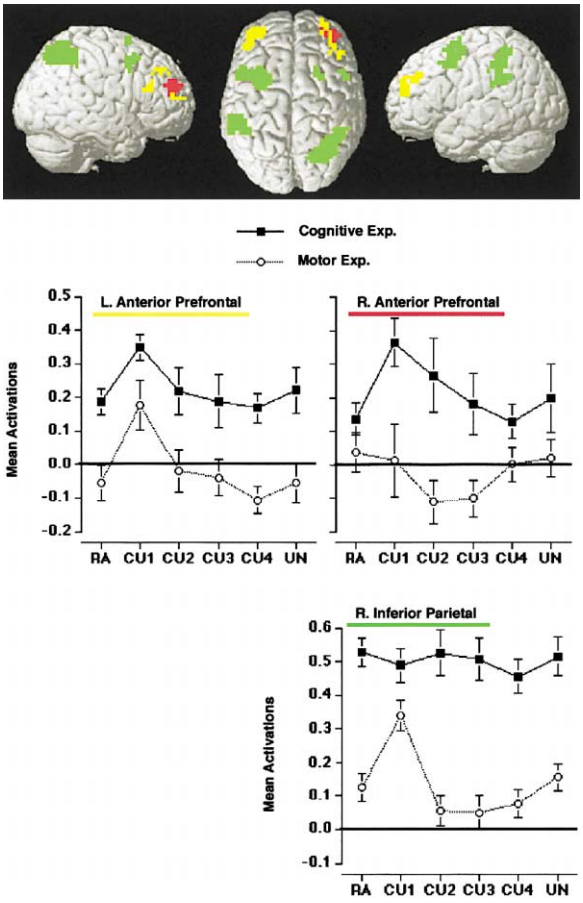

Figure 6. Topography (Top) and Activation Profiles (Bottom) of Controlled-Learning Effects

Yellow, joint effects (activation in the left prefrontal cortex peaks at $x, y, z = -36, 56, 24$; BA 10) . Green, motor-specific effects are shown. Red, cognitive-specific effects are shown (activation peaks at $x, y, z = 36, 48, 20$; BA 10). See Figure 3 for graph legends. All green regions exhibited similar activation profiles.

whether subjects were learning motor or cognitive sequences. These nonspecific cue-learning effects were related to processing predictable events common to both experiments, i.e., the sequences of external cues themselves. Since those cues provided feedback information about subjects' expectations in motor and cognitive sequences, nonspecific cue-learning effects reflected the increasing proportion of cues that confirmed subjects' expectations. Thus, our data suggest that the whole anterior medial fronto-striatal circuit including the VS and AMPC is engaged in processing nonspecific internal reinforcement signals that drive the acquisition of action sequences. This interpretation is consistent with electrophysiological studies in monkeys indicating that neurons in the VS (Schultz et al., 1992; Shidara et al., 1998) and in the anterior cingulate cortex (Shidara and Richmond, 2002) respond to rewards or events that predict future rewards. The functional segregation reported here, however, indicates that the VS and AMPC are further specialized in using those internal reinforcement signals for building motor and cognitive sequences respectively, i.e., for evaluating specifically subjects' expectations that develop in either the motor or cognitive domains.

The present results may clarify some apparent discrepancies between previous studies. On the one hand, several neuroimaging studies in humans have emphasized the role of the VS and AMPC in processing external signals with intrinsic emotional and incentive valence (review in Bush et al., 2000; Delgado et al., 2000). On the other hand, other neuroimaging studies revealed that these brain structures could also be engaged in learning behaviors even when external signals contained no intrinsic emotional or incentive valence (Doyon et al., 1996; Grafton et al., 1995; Jueptner et al., 1997; Koechlin et al., 2000). Indeed, our results suggest that in those latter studies, the VS or AMPC were engaged, because external signals provided information about the reliability of subjects' expectations and resulted in the computation of internal reinforcement signals driving learning.

Our findings support current theories proposing that learning is induced by the prediction error, i.e., the match or mismatch between internal expectations and external signals (Hertz et al., 1991; Schultz et al., 1997). Furthermore, theoretical works on learning mechanisms make the distinction between supervised and reinforcement learning processes (Dickinson, 1980; Hertz et al., 1991). In reinforcement processes, match and mismatch signals are nonspecific and evaluative, indicating only whether subjects' predictions are accurate, whereas in supervised processes, match and mismatch signals are evaluative, specific, and instructive, indicating additionally the correct actions that should have been performed. This theoretical distinction provides a possible computational interpretation of specific and nonspecific cue-learning effects observed in the present study. The regions exhibiting nonspecific cue-learning effects in the VS and AMPC may be related to reinforcement processes restricted to processing cue information and computing nonspecific evaluative signals that are broadcast to various brain systems. In contrast, the regions in the VS and AMPC exhibiting specific cue-learning effects may be related to supervised processes computing specific, instructive match/mismatch signals in the motor and cognitive domains, respectively. Accordingly, this interpretation suggests that reinforcement and supervised learning processes interact together in the VS and AMPC to optimize the acquisition of motor and cognitive action sequences, respectively. This interpretation, as well as the finding of specific and nonspecific cue learning effects in both structures, is consistent with various functional classes of neurons that have previously been described most notably in the VS (Graybiel and Kimura, 1995; Schultz et al., 1995).

The VS and AMPC were found to exhibit similar cue-learning effects. The fMRI data also revealed some differences regarding the response profiles of each structure. In the striatal region exhibiting motor-specific cue-learning effects, mean activations in the cognitive experiment remained below the baseline, but those deactivations were found to decrease significantly with learning ($F[3, 21] = 4.9$, $p < 0.01$; Figure 5A). Conversely, the AMPC regions showing cognitive-specific cue-learning effects exhibited no variation of activations during motor sequence learning ($F[3, 21] < 1$; Figure 5B). This asymmetry may result from the unidirectional projections that directly connect the AMPC to the VS (Alexander et al., 1986; Haber et al., 1995), suggesting that the AMPC works as a "master device" modulating the functional involvement of the VS. This possible hierarchical organization may provide a brain mechanism for building motor sequences from cognitive sequences, e.g., when a cognitive sequence is always performed in the same behavioral context resulting in the repetition of the same motor acts.

The present results indicate that motor and cognitive action sequences are acquired and processed as distinct internal representations. Consistent with previous human and nonhuman studies (Gordon et al., 1998; Jenkins et al., 1994; Shima and Tanji, 2000; Tanji and Shima, 1994), the execution of fixed motor sequences relative to baseline was found to engage specifically the SMA regardless of the presentation of external cues. Conversely, the execution of fixed sequences of cognitive tasks when compared to the execution of the same tasks in a random order was found to engage specifically Broca's area and the adjacent left prefrontal cortex, regardless of the presentation of external cues. This is consistent with previous results showing that patients with left-sided, but not right-sided, frontal lesions were impaired in switching predictively between cognitive tasks (Rogers et al., 1998). Given that Broca's area is known to subserve the syntactic processing of human language (e.g., Just et al., 1996), our finding may suggest that, in contrast to motor sequences, sequential patterns underlying cognitive sequences are preferentially represented and processed in a language-like syntactic format.

Furthermore, both the SMA and Broca's area were engaged from the beginning to the end of the learning sessions, while subjects were learning or reproducing fixed action sequences. Such activation profiles indicate that both structures were involved in encoding, storing, and retrieving sequential patterns. Thus, the present results suggest that the SMA and Broca's area mediate the internal generation of motor and cognitive actions, respectively, and subserve the storage of the evoked actions that were confirmed by evaluation processes in the VS and AMPC. This view is supported by the known anatomical organization of the frontal cortex, since the SMA is reciprocally connected to the striatum (Alexander et al., 1986), while the AMPC is reciprocally connected to the lateral prefrontal cortex (Barbas and Pandya, 1989).

Finally, the present study shows that learning explicit action sequences engage explicit control and evaluation processes subserved by distinct brain networks. In particular, consistent with previous studies (Jenkins et al., 1994; Strange et al., 2001), frontopolar regions were found to mediate explicit control processes engaged in motor and cognitive learning. It is worth noting that similar frontopolar regions were shown to subserve branching processes, i.e., multitasking processes required when subjects switch back and forth between foreground and background tasks (Koechlin et al., 1999). Indeed, branching processes are likely to be engaged in explicit sequence learning, when subjects have to execute series of actions on the one hand, while searching for and inferring consciously, underlying sequential patterns on the other hand. Further comparisons of frontopolar activations between motor and cognitive experiments mainly reveal that frontopolar regions disengaged gradually in the cognitive experiment but returned abruptly below the baseline level during the early phase of motor learning sessions (Figure 6), a difference that may explain the quadratic decrease of reaction times observed only during motor sequence learning (Figure 2). In addition, the gradual recruitment of the VS and AMPC during learning sessions suggests that evaluation processes implemented in those regions are engaged whatever subjects' expectations result from explicit control processes occurring early in learning or from implicit generation processes occurring later when behavior becomes more automatic. This interpretation is supported by previous studies showing that the VS was involved in the implicit or explicit acquisition of motor sequence (Doyon et al., 1996; Grafton et al., 1995). An unresolved issue, however, is whether the acquisition

of cognitive action sequences and the related involvement of evaluation processes in the AMPC may also occur implicitly, when subjects have no explicit knowledge of action sequences.

In summary, the results show that the AMPC was engaged in learning sequences of cognitive tasks in the same way that the VS was recruited in learning sequences of body movements. Specifically, we found evidence that the AMPC is recruited to evaluate the expectations of future events that subjects develop for building cognitive action sequences, while the VS is involved in evaluating the expectations of future events that subjects develop for building motor action sequences. This functional segregation shows that beyond the execution of motor acts, the AMPC is selectively involved in evaluating the relevance of cognitive goals that subjects intend to achieve, suggesting that the AMPC may be critical for the human ability to learn and build behavioral plans that extend beyond motor programs and that are usually referred as to cognitive schemes, procedures, or strategies (Fuster, 1989; Grafman, 1995). Our findings may help to clarify the conjunctions and dissociations between motor and cognitive deficits observed in several neurological and neuropsychiatric disorders affecting the AMPC and the striatum, such as Parkinson's disease and schizophrenia (Benes, 1993; Brown and Marsden, 1988; Devinsky et al., 1995; Rogers et al., 1998). More generally, our study indicates that the VS and AMPC in humans are key components of a subcortical-cortical loop circuit that subserves hierarchically distinct evaluative processes mediating the human ability to build behavioral plans, ranging from motor to cognitive action plans

Experimental Procedures

Subjects

Subjects were four females and four males aged 20–29 years. The order of experiments was counterbalanced across subjects and genders. Subjects provided written informed consent, and the protocol was approved by the National Institutes of Health, Bethesda, MD.

Behavioral Protocol

Prior to each experiment, subjects were told whether they had to learn motor or cognitive sequences. In each experiment, subjects were explicitly asked to learn six distinct action sequences in six separate sessions. Stimuli were series of successively presented colored letters (lower- and upper-case letters pseudo-randomly chosen from the word "tablet," 500 ms duration, 2000 ms stimulus-onset-asynchrony). Subjects responded by pressing left or right hand-held response buttons (Figure 1). Each session was divided into nine successive experimental blocks intermixed with baseline blocks. Each block was preceded by a distinctive visual signal. In the experimental blocks (including 16 successive letters; block duration, 34s), the color cue indicated the finger that subjects had to move (motor experiment) or the task that they had to perform on each letter (cognitive experiment). In the random condition, color cues were presented in random sequences. In the cued condition, color cues were presented in fixed sequences (of four items) so that subjects learned either the associated task (cognitive experiment) or finger (motor experiment) sequences. In the uncued condition, color cues were turned off, but subjects had to reproduce the same cognitive or motor sequences they just learned in the cued blocks. In the baseline blocks (including nine successive letters; block duration, 20s), color cues were turned off, and subjects had to press both left and right buttons regardless of letter identity (detection task). In all blocks, the proportions of left and right responses were always 50%. Letters were distributed in equal proportion between colors.

Data Acquisition

Each experiment was administered in six successive learning sessions using the EXPE software package (Pallier et al., 1997). In each session, a new sequence was learned. Before each experiment, subjects were trained by practicing additional learning sessions with different sequences not used in the scanner. In each experiment, a 1.5 GE signa whole-body and RF coil scanner was used to perform a high-resolution structural scan for each subject followed by 6 series of 178 functional axial scans acquired during each of the 6 learning sessions (TR, 3 s; TE, 40 ms; flip angle, 90°; FOV, 24 cm; acquisition matrix, 64×64; number of slices, 18; and thickness, 6 mm). Then, the first four scans of each functional series were discarded and all fMRI data were processed using the SPM99 software package (http://www.fil.ion.ucl.ac.uk/spm/). Standard linear image realignment, linear normalization to the stereotaxic Talairach atlas (MNI template, sampling voxel size, $4 \times 4 \times 4$ mm^3) (Talairach and Tournoux, 1988), spatial (3D Gaussian kernel, 10 mm), temporal smoothing (Gaussian kernel, 4000 ms), and mean MR signal normalization across scans were successively performed for each subject.

Statistical Analysis

The data for all subjects were pooled together, and statistical parametric maps were computed from local MR signals using a linear multiple regression analysis with conditions (modeled as box-car functions convolved by the canonical hemodynamic response function), scanning series, and their linear trends as covariates (Friston et al., 1991).

Statistical analyses based on a fixed-effect model were first performed to evaluate the fit between the regression model, the related contrasts (sequence, cue-learning, and controlled-learning effects), and local MR signals. In all these analyses, only regions formed by more than eight contiguous significant voxels (512 mm^3; $p < 0.01$, corrected) were reported in order to minimize type I errors. In accordance with our prediction and to minimize type II errors, fMRI data was first analyzed in the volume of interest (VOI), including the basal ganglia and the anterior medial frontal cortex (VOI in Talairach coordinates: -30 mm $< x <$ 30 mm; -25 mm $< y <$ 70 mm; -20 mm $< z <$ 20 mm). To account parametrically for linear learning effects as revealed by behavioral performances (Figure 2), the cued condition was broken down into four covariates (Cu1 = block #2, Cu2 = block #3, Cu3 = block #4, and Cu4 = blocks #5 and #7; see Figure 2, right). In each experiment, the learning effect was computed as linearly increasing activations in the cued condition (-0.9*Cu1 + -0.3*Cu2 + 0.3*Cu3 + 0.9*Cu4 > 0). A cue effect was computed as postlearning activations in the cued condition (Cu4) compared with the uncued condition (Un) and the baseline (Ba) (Cu4 > Un and Ba). The cue-learning effect was then computed by selecting regions showing significant learning and cue effects averaged together within the VOI ($Z > 3.73$, $p < 0.05$, corrected for multiple comparisons in the VOI) and exhibiting, in addition, significant learning and cue effects separately ($Z > 2.33$, $p < 0.01$, uncorrected). All voxels with significant activations in the uncued condition compared to the baseline were excluded ($Z > 1.69$, $p < 0.05$, uncorrected). A subsequent whole-brain analysis was performed to investigate cue-learning effects outside the VOI (the corrected statistical threshold, $p = 0.05$, corresponded then to $Z = 4.13$).

The sequence effect was examined in the whole brain and was computed as postlearning activations in both the cued and uncued conditions compared to the baseline condition (0.5*Cu4 + 0.5*Un > Ba, $Z > 4.13$, $p < 0.05$, corrected). All voxels with significantly distinct activations in the cued and uncued conditions were excluded ($F > 3.84$, $p < 0.05$, uncorrected). In the cognitive experiment, we reported only voxels that showed, in addition, significant activations in the cued and uncued conditions compared to the random condition (0.5*Cu4 + 0.5*Un > Ra, $Z > 2.33$, $p < 0.01$, uncorrected), thereby excluding regions involved only in executing or switching between cognitive tasks. In the motor experiment, consistent with previous fMRI studies (Van Oostende et al., 1997), no region exhib-

ited significant activations in the cued and uncued conditions compared to the random condition.

The controlled-learning effect was also examined in the whole brain. We first computed an early-learning effect (activations in the first cued condition compared to the baseline and random conditions, Cu1 > Ba and Ra) and a decreasing effect (decreasing activations during learning, 0.9*Cu1 + 0.3*Cu2 + −0.3*Cu3 + −0.45*Cu4 + −0.45*Un > 0). Then, the controlled learning effect was computed by selecting regions showing significant early-learning and decreasing effects averaged together ($Z > 4.13$, $p < 0.05$, corrected) and exhibiting, in addition, significant early-learning and decreasing effects separately ($Z > 2.33$, $p < 0.01$, uncorrected).

Joint cue-learning, sequence, and controlled-learning effects over the motor and cognitive experiments were computed as in each experiment but using the minimum-field statistics over the two experiments (conjunction analysis) (Worsley and Friston, 2000).

Finally, in order to account for between-subjects variability and to allow statistical inferences at the population level, all voxels showing significant cue-learning, sequence, or controlled-learning effects as described above were subsequently analyzed using a random-effect model. In these random-effect analyses, cue-learning, sequence, and controlled-learning effects were computed in the same way as above (all voxel-wise thresholds, $p < 0.05$; cluster-wise thresholds, $p < 0.01$, corrected for multiple comparisons over the search volumes). The random-effect analyses confirmed all significant activations found in the fixed-effect analyses. The only exception is a right lateral frontopolar region exhibiting a significant motor-specific controlled-learning effect in the fixed- but not in the random-effect model.

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